

Clinical trials on human beings: ethics “requirements” and available framework

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Introduction

“Human being” is fragile and precious, but that same “human being” is also rash and egoistically avid; he is avid for learning, avid for discovering always more and more, often to the detriment of others¹. Some acts committed by men throughout the last centuries for the sake of a science are awful, that’s why needs of red lines are real and justified. A balance must be found between the interests of science and society and the well-being and dignity of human beings. Professor Jean Bernard emphasized in this respect that even if clinical trials might appear somehow immoral², they are nevertheless necessary for the science’s progress. In this respect, clinical trials represent the gold standard for transposing biomedical theory into practical treatment and prevention of disease. Clinical trials have led to curative treatments for a number of cancers, prolonged life expectancy for others (breast, colorectal) and new treatments with fewer and less severe side effects³. E. Abadie reminds that “clinical research is indispensable for determining the safety and efficacy of drugs in human. It provides the scientific basis for rational drug usage. (But) Methodology of clinical trials can raise some ethical issues”⁴. That’s why we should highlight the importance of scientific and ethical concerns together with man’s dignity.

This consciousness’s worrying in order to conciliate between interest and progress of science and safeguarding of man’s dignity is embodied by several official texts whereby the accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine. In fact, “society can neither tolerate experiments with human beings in the name of research nor ignore the implications of research directly or indirectly devoted to eugenics”⁵.

¹ A. Aouij-Mrad, « Droit Comparé : Normes et Pratiques », in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.46.

² Professor Jean Bernard wrote: « La méthode des essais comparés est à la fois moralement nécessaire et nécessairement immorale », mentioned by Amel Aouij-Mrad, in « *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique* », IX Annual Conference, Tunis, September 30th 2005, p.46.

³ NIH 1990 & 1991; Fisher et al. 1989 & 1997; Perez et al. 1998, mentioned by Meredith L. Kilgore, *Effects of Trial Design on Participation and Costs in Clinical Trials*, with an Examination of Cost Analysis Methods and Data Sources, Pardee rand Graduate School, 2004, RAND Corporation, p.1.

⁴ E. Abadie, “Ethics and clinical trials”, in *L’Encéphale*, 16 (4), pp.275-6, <<http://www.researchgate.net/author/>>

⁵ Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D., “Ethical and

During the last decades, and apart from the problem of consciousness arisen by clinical trials, another tremendous issue related to globalization is to be taken seriously. Indeed, Clinical research is undergoing the same globalization process as other industries, “pharmaceutical and device companies have embraced globalization as a core component of their business models, especially in the realm of clinical trials. This phenomenon raises important questions about the economics and ethics of clinical research and the translation of trial results to clinical practice: Who benefits from the globalization of clinical trials? What is the potential for exploitation of research subjects? Are trial results accurate and valid, and can they be extrapolated to other settings?”¹.

Back to the historical roots, clinical trials were first introduced in The Canon of Medicine in 1025 B.C., considered as the guide for practical experimentation in the process of discovering and proving the effectiveness of medical drugs and substances². The principles laid out in the document form the basis of modern clinical trials. Centuries after, to put an end to man’s insanity was elaborated first the Code of Nuremberg, and few years later, the Helsinki Declaration of 1964. The Helsinki Declaration (DoH)³ of the World Medical Association is the most mentioned reference. It has been revised several times, last revision dates October 2008, and has risen to a position of prominence as a guiding statement of ethical principles for doctors involved in medical research.

The above mentioned text is not the only one pursuing this objective, it is also useful to mention the Treaty establishing the European Community, and in particular Article 95 thereof, Opinion of the Economic and Social Committee 1995⁴, the European Convention for the protection of human rights and of the dignity of the human being with regards to the applications of biology and medicine, elaborated within the framework of the Council of Europe on November 19th, 1996⁵. Almost, all texts endorse the DoH as the accepted basis for clinical trials ethics.

Today, the main text applied to the issue of clinical trials is Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of States’ Members relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Scientific Implications of the Globalization of Clinical Research”, in *The New England Journal of Medicine*, vol.360, February 19, 2009, number 8, pp. 816-823.

¹ Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D., “Ethical and Scientific Implications of the Globalization of Clinical Research”, op. cit.

² Toby E. Huff (2003), *The Rise of Early Modern Science: Islam, China, and the West*, Cambridge University Press, p. 218.

³ The World Medical Association's Declaration of Helsinki was first adopted in 1964. In its 40-year lifetime the Declaration has been revised five times and has risen to a position of prominence as a guiding statement of ethical principles for doctors involved in medical research. The most recent revision, however, has resulted in considerable controversy, particularly in the area of the ethical requirements surrounding placebo-controlled trials and the question of responsibilities to research participants at the end of a study. Robert V Carlson, Kenneth M Boyd and David J Webb, “The revision of the Declaration of Helsinki: past, present and future” in *British Journal of Clinical Pharmacology*, 57 (6), June 2004, pp.695–713.

⁴ Opinion of the Economic and Social Committee, OJ C 95, 30.3.1998, p. 1.

⁵ As well as the Proposal from the Commission, OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.

The Directive was modified several times in order to put the red line to grave and unpredictable consequences of clinical trials on human being¹.

But first, and before going deeper and further with the analysis of the legal framework, let's check what is meant by "clinical trials"? The identification of the notion of clinical trials needs of course to refer primary to the conventional framework which will be dealt with more largely further. We shall at this stage of the introduction highlight the difficulties and the complexity of the definition as well as the attempts to harmonize it, particularly if we keep in mind that synonyms for "clinical trials" include clinical studies, research protocols and clinical research.

Clinical trials are defined in Article 2 of Directive 2001 as: "(a) any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; this includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State". Clinical trials appear as a critical tool for determining which preventive, diagnostic, and/or therapeutic interventions have value and to compare alternative treatments. As the number and complexities of trials increase and as new technologies emerge and become more sophisticated, it is important to evaluate current clinical trial system to ensure that it is functioning commensurate with the scientific and technical knowledge at hand².

After duly defining keys words from the legal and comprehensive point of view, we shall remind that some scholars do consider clinical trials also as part of customary framework. Clinical trials are part of a customary minimum standard that reached today its autonomy, till becoming an independent standard.

It is also relevant to specify that there is not a single type of clinical trials; scholars enhance the existence of different types of clinical trials. Indeed, several classifications of clinical trials exist; they depend on the classification's criterion selected:

One way of classifying clinical trials is by the way researchers behave. We distinguish hence between observational study and interventional study. In an observational study, the investigators observe the subjects and measure their outcomes. Researchers do not actively manage the experiment. In an interventional study, investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment and then measure how the subjects' health changes³.

A second way of classifying clinical trials is through the criterion of their purpose. European researchers distinguish between treatment trials, prevention trials, screening trials and quality

¹ Last modification dates 2006 when that Directive has been amended by Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, Official Journal L378, p.1, dated 27/12/2006.

² Clinical trials, transformation initiative,
<<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/SpotlightonCPIProjects/ucm083241.htm>>

³ S.C. Chow & J.P. Liu, *Design and Analysis of Clinical Trials: Concepts and Methodologies*, Wiley, NY, 2004.

of life trials. “Treatment trials test new treatments (like a new cancer drug, new approaches to surgery or radiation therapy, new combinations of treatments, or new methods such as gene therapy). Prevention trials test new approaches, such as medicines, vitamins, minerals, or other supplements that doctors believe may lower the risk of a certain type of cancer. These trials look for the best way to prevent cancer in people who have never had cancer or to prevent cancer from coming back or a new cancer occurring in people who have already had cancer. Screening trials test the best way to find cancer, especially in its early stages. Finally, quality of Life trials (also called Supportive Care trials) explore ways to improve comfort and quality of life for cancer patients”¹.

But the U.S. National Institutes of Health classifies trials into five (5) different types also referring to the same criterion, namely the criterion of purpose. In addition to the European quadruple type’s classification, a fifth one is the compassionate use trials². The latter type provides experimental therapeutics prior to final Food and Drug Administration³ (FDA) approval to patients whose options with other remedies have been unsuccessful. Usually, case by case approval must be granted by the FDA for such exceptions.

In addition to the already mentioned classifications, point 14 of the Directive Preamble distinguishes between commercial clinical trials and non-commercial clinical trials. It is the intention behind the conducting of clinical trials which prevails here. Non-commercial trials are privileged by both patients and doctors, “non-commercial clinical trials offer a valuable method of defining the best place of new treatment options in medical practice”⁴.

Another criterion is the one which relies on the process’s description. It is particularly highlighted in case of clinical trials involving cancer diseases. Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites. States current practices diverge considerably on the rules governing the beginning and the conduct of clinical trials; moreover, conditions to be fulfilled in order to carry out clinical trials vary widely. Nevertheless, clinical trials do follow the same procedure. Indeed, most clinical research that involves the testing of a new drug progresses in an orderly series of steps, called phases”. Hence, most clinical trials are classified into one of four phases⁵:

“Phase 1 trials: These first studies on “healthy volunteers”⁶ evaluate how a new drug should be given (by mouth, injected into the blood, or injected into the muscle), how often, and what dose is safe. A phase 1 trial usually enrolls only a small number of patients, sometimes as few as a dozen.

Phase 2 trials: A phase 2 trial continues to test the safety of the drug, and begins to evaluate how well the new drug works”⁷. Trials conducted in phases 1 and 2 are typically small, their

¹ A summary extract from the article entitled “What are clinical trials?” available in the website of Palo Alto Medical Foundation, <<http://www.pamf.org/cancer/care/trials/whatare.html>>

² Glossary of Clinical Trial Terms, (American) National Institute of Health [Clinicaltrials.gov](http://clinicaltrials.gov)

³ Food and Drug Administration is the US regulatory agency which is the authority concerned at the federal level.

⁴ “Clinical Trials Directive still hampering academic medical research”, report on Dr M. Hartmann’s criticism of the European Directive <http://www.eurekalert.org/pub_releases/2007-09/eccc-ctd092707.php>

⁵ Ph. Unger, “Etat des lieux des essais de nouveaux médicaments en Tunisie : point de vue du promoteur”, in « *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique* », IX Annual Conference, Tunis, September 30th 2005, p.30.

⁶ Ph. Unger, “Etat des lieux des essais de nouveaux médicaments en Tunisie : point de vue du promoteur”, op. cit., p.30.

⁷ <[http://www.cancer.gov/clinical trials/](http://www.cancer.gov/clinical%20trials/)>

purpose is to evaluate dosage schedules, measure pharmacokinetics, and provide preliminary information on adverse events.

Phase 3 trials: “These studies test a new drug, a new combination of drugs, or a new surgical procedure in comparison to the current standard. A participant will usually be assigned to the standard group or the new group at random (also called randomization). Phase 3 trials often enrol large numbers of people and may be conducted at many doctors' offices, clinics, and cancer centres nationwide”¹. Indeed, the term “clinical trials” is most commonly associated with the large, randomized studies typical of Phase 3, but many clinical trials are small. Phase 3 trials are designed to determine the safety and efficacy of the treatment under investigation. They may be “sponsored” by single physicians or a small group of physicians, and are designed to test simple questions. Indeed, the trial sponsor may be a private company, a government health agency, or an academic research body such as a university

In addition, after a treatment has been approved and is being marketed, the drug's maker may study it further in a phase 4 trial. The purpose of phase 4 trials is “to evaluate the side effects, risks, and benefits of a drug over a longer period of time and in a larger number of people than in phase 3 clinical trials. Thousands of people are involved in a phase 4 trial”².

Despite the complexity and all the cautiousness that encompass any clinical trial, its success is not ensured. The success of the clinical trial system will depend on continued public confidence in its safety, integrity, and transparency. This paper hence tries to question in filigree whether there is a universal minima ethics to clinical trials through the existing framework, wondering if this framework will prove unusable or useable in dealing with clinical trials' issues. Within this paper, two themes will be addressed. The first theme addresses the legal framework available in different countries (Part I) whereas the second will address the institutional framework, acting as a genuine “garde-fou” or parapets for clinical trials (Part II).

I- The legal framework

Before a drug is available, clinical trials of new drugs on humans are used in order to conduct a rigorous and necessary evaluation in compliance with scientific, ethics and legal rules. Some legal systems in Europe, and in other countries such as Tunisia, require for the development of a new drug to necessarily respond to a series of standards and principles regulating the stages of research and the rights of research subjects and the obligations of the investigator.

The testing of drugs should be done normally in compliance with legislative rules, strict regulations, and clear background. These legal systems are necessary to meet the most stringent requirements and conform to international conventions and declarations. The international standards set the foundations of main ethics and legal principles to be observed by different national laws; they appear as unavoidable markers.

If international requirements are the same, the internal legislation of each country may differ. From the beginning, it is important to present the legal texts relating to clinical trials by referring to some examples from different countries including the Tunisian one. Relevant

¹ <[http://www.cancer.gov/clinical trials/](http://www.cancer.gov/clinical%20trials/)>

² Phases of clinical trails, Free Press Release, November 14, 2008, <<http://www.free-press-release.com/news/200811/1226646201.html>>

legislation may be presented in two main ideas. Clinical trials' legal texts have specific features (A) and are rigorous in their content (B).

A - Specific features

Texts regulating clinical trials vary. Hence, it is worthy to consider those prevailing at the international level (1), the European one (2) and the ones applied at national level (3).

1 - at the international level

It is important to mention that the problem of experimentation on human beings arose from precisely after the Second World War, especially after the discovery of the barbaric acts carried out by Nazi doctors. The Nuremberg Tribunal which was held in 1947 in order to incriminate Nazi doctors had to cope with the issue of legal and ethics experimentation on humans. The court outlined the famous rules to be observed in any human experimentation and which can be chiefly summarized as “the prohibition of experimentation on human beings without their voluntary consent”. Later on, the Nuremberg Code was supplemented by several international texts:

- The Universal Declaration of Human Rights, adopted by the UN General Assembly in its resolution dated 10 December 1948, which guarantees the protection of the human person and particularly its article 25 “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control”.

- The Declaration of Helsinki of the World Medical Association (WMA) on ethical principles for medical research involving human subjects adopted by the 18th General Assembly of the WMA in June 1964 and which is regarded as mentioned above as the Reference to inspire national legislation. Some important paragraphs from the Helsinki Declaration are briefly summarized below:

“13. The protocol for a clinical trial should be reviewed by an independent ethical review committee. The researchers must report any serious adverse events to this committee.

16. The design of all studies should be publicly available.

17. Investigations should be ceased if the risks are found to outweigh the potential benefits.

19. The research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. Participation in a trial must be voluntary and participants must be informed.

22. Physicians should obtain freely-given informed consent from each participant.

24. Subjects who cannot provide informed consent themselves, for example children, should only be included in the research cannot be performed on other subjects instead.

29. The benefits, risks, burdens and effectiveness of a new therapy should be tested against those of the best currently available therapy. Placebo-controlled trials are only allowed if no proven therapy exists or under special circumstances.

30. At the conclusion of the study, all trial participants should be assured access to the best proven therapy identified by the study. Post-trial access arrangements must be described in the trial protocol”¹.

¹ SOMO briefing paper on ethics in clinical trials, Examples of unethical trials: Feb 2008, <<http://www.somo.nl>>

The above mentioned Declaration was last amended on October 2008 strengthening “the previous version in some respects and weakens it in others. The most salutary improvement is in the paragraph that stipulates when it is ethically acceptable to use placebos in a control arm of a randomised, controlled clinical trial”¹. In this respect, according to scholars, “along with other paragraphs that gave rise to some controversy, the one that attracted most attention was the new Paragraph 29, which basically reiterated the statement in the 1996 version: “The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists”². Another change that deserves to be mentioned is “the addition, for the first time, of a requirement that sponsors register clinical trials”. Paragraph 19 provides that “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject”. As highlighted by commentators “the virtue of this requirement is that it makes transparent just which clinical trials fail to reach a successful conclusion, either because of demonstrated lack of safety or absence of efficacy”³.

- The United Nations Covenants on Civil and Political Rights and on Economic, Social and Cultural Rights of 16 December 1966. In compliance with the first Covenant, it is forbidden to subject any person to medical or scientific experimentation without her free consent. Article 7 stipulates “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation”. As far as the United Nations Covenant on Economic, Social and Cultural Rights is concerned, it is relevant to point out to the admission of the right to benefit of the “best physical and mental health status that he (a person) may achieve”.

- The Manila Declaration of 1981 which calls for special protection measures for certain categories of persons whose capacity to consent is questionable, such as children, prisoners, and people with mental deficits and even pregnant women and nursing mothers. The Manila Declaration is the fruit of huge efforts undertaken by CIOMS, namely the Council for International Organizations of Medical Sciences. It is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. The main objectives of CIOMS are: To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary; To maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO; and to serve the scientific interests of the international biomedical community in general. The outcome of the CIOMS/WHO undertaking was, in 1981, the Declaration of Manila, and, in 1982, the « Proposed International Ethical Guidelines for Biomedical Research Involving Human subjects ». These documents reflect both the conditions and needs of biomedical research in developing countries, and the implications for multinational or transnational research in which they may be partners. We shall finally mention chapter V entitled “scientific research” of the Oviedo Convention and its Protocols although the Convention is not yet applied.

¹ Ruth Macklin, Editorial, “the Declaration of Helsinki: another revision”, in *Indian Journal of Medical Ethics*, Vol. VI, n°1 January-March 2009, p.2.

² Ruth Macklin, Editorial, “the Declaration of Helsinki: another revision”, op. cit.

³ *Ibid*, p.3.

2 - at the European level

It is praiseworthy to mention in this regard two famous texts:

- Directive 2001/83/EC establishing a Community Code on medicinal products for human use. This Directive refers to the Helsinki Declaration in its Annex I, part IV B) “All clinical trials are conducted in accordance with the ethical principles laid down in the current Declaration of Helsinki”.

- Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use adopted on 4 April 2001. The Directive must be transposed by Member States into national law by May 2003 and be implemented before May 2004. It aims to identify principles to protect the subjects participating in trials and to establish best clinical practice to test drugs (including cellular and gene therapies). This Directive was amended on 2006¹. The Directive Preamble (point 2) emphasizes that “the accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data”.

It is relevant to remind that the European Union is not directly responsible for regulating research in general, an area which lies under the responsibility of Member States. However, the Union is responsible for authorizing the marketing of drugs on the market. As explained further, this authorization is issued by the Commission on the basis of reports prepared by the European Agency for the Evaluation of Medicinal Products (EMA) and may be refused in case of non-compliance with the ethical principles found in clinical trials.

3 - at national level

Two legal frameworks will be dealt with: the French one and the Tunisian one, keeping in mind the strong ties between both legislations due to the fact that Tunisian law remains greatly influenced by the French one.

- ***French legislation***: In France, the protection of the person in case of medical research is provided by the Huriet-Sérusclat Law of the 20th December 1988² which has most recently been amended. Thanks to the Huriet-Sérusclat Law, France has a law governing biomedical research. The main points of this legal framework are: the protection of persons; assessment of risk / benefit ratio of research; the need for information and free and informed consent of individuals.

In France, when clinical trials are to be applied experimentally to human beings, they must adhere to the principles stipulated by the Huriet-Sérusclat law on biomedical research. The spirit of the Huriet Law was clearly enunciated in J.F. Mattei's report: “the application of the

¹ Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, Official Journal L378, page 1 dated 27/12/2006.

² Huriet Law n°88-1138 of 20 December 1988 concerning the protection of persons lending themselves to biomedical researches.

law does not depend on the nature of the proposed product or technique; it aims to protect persons and to that end establishes rules that are to govern the implementation of any new technology among humans in general”¹. The law stipulates that “trials or experiments organised and practised on human being with the aim of developing biological or medical knowledge” are authorized in the conditions foreseen into the present book and are indicated below by the terms “Biomedical Research” (art. L. 209-1). The objective is to allow the biomedical research (essentially experimentation of medicines) to break in the provisions of the Penal code according to which “No harm can be caused to the integrity of the human body unless for the purpose of therapeutic necessity”.

In 2004, France carried out the transposition of European Directive No. 2001/20/EC of April 4th, 2001 on the approximation of laws, regulations and administrative provisions of Member States concerning the implementation of good clinical practice in the conduct of clinical trials of medicines for human use. The Public Health Act of August 9th, 2004 and the implementing decree of April 26th, 2006 now govern biomedical research.

- **Tunisian legislation:** According to Tunisian law, the inviolability of human body is a fundamental principle which enjoys a constitutional value in compliance with the provisions of Article 5 of the Tunisian Constitution which provides that “the Tunisian Republic guarantees the inviolability of the human person”². Despite this constitutional provision, Tunisian scholars consider that “although this issue is crucial, medical experimentation on human beings in Tunisia has not been dealt with thoroughly and in compliance with a specific legislation related to the protection of persons who are subjects to biomedical research like the French experience through Huriet-Serusclet Law dated December 20th 1988, relating to the protection of persons who are subjects to biomedical research”³.

In the absence of a specific law concerning medical experimentation on human beings, it is important to mention Law n°85-91 dated November 22nd 1985 regulating the manufacture and registration of drugs for human medicine. This law expressly “dismisses the issue to the executive branch, the latter has the task of regulating the various modalities of the medical or scientific experimentation through regulations”⁴. Article 7 of the above mentioned Law provides that “(...) the medical or scientific experimentation whose ways of implementation are established by decree, must be implied in compliance with the principles of the International Convention on Human Rights as well as with the rules that govern medical deontology”⁵.

¹ J.F. Mattei, « Bilan de l’application de la loi Huriet », Report to the prime Minister on Biomedical ethics in France, *Ministry of Social Affairs, Ministry of Research and Higher Education*, 1993, pp. 49-69; mentioned by G. Moutel, N. Leroux, C. Hervé, “Analysis of a survey of 36 French research committees on intracytoplasmic sperm injection”, *Laboratoire d’Ethique Médicale, de Droit de la Santé et de Santé Publique* (1998), < <http://www.hal.inserm.fr/inserm-00120208/en/>>

² Article 5: « The Tunisian Republic guarantees the inviolability of the human person (...) », The Tunisian Constitution adopted by Law no 59-57 dated June 1st 1959, JORT n°30 June 1st, 1959 original version in arabic, page 746.

³ M. K. Jamoussi, « Le cadre juridique et réglementaire des essais cliniques de nouveaux médicaments chez l’Homme en Tunisie », in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30 2005, p.13; see also M. K. Charfeddine, « La question de l’actualisation des textes relatifs aux essais cliniques », *ibid*, p.74.

⁴ M. K. Jamoussi, *op. cit.*, p.13.

⁵ Tunisian Law n°85-91 dated November 22nd 1985 relating to the manufacture and registration of drugs for human medicine, JORT n°84 dated 26-29 November 1985, p.1584.

It is Regulation and not Law which governs clinical trials in Tunisia. In this respect, “medical experimentations are regulated by a regulation, namely, Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine”¹. According to the first article of this Decree, “the medical or scientific experimentation of drugs for human medicine must be held in compliance with international conventions on health and human rights, duly ratified by Tunisia, and with rules of medical deontology and ethics relating to experimentation on human”². But Tunisian scholars keep wondering about this dismissal of the legislative branch in favor of the executive one and point out to the prejudice that might encounter the clinical trials issue if it doesn’t fall under the jurisdiction of a specific legislation, indeed “the adoption of texts into a legislative framework represents in itself a guarantee which simple regulations cannot provide for”. Tunisian scholars also remind that the “Law’s procedure” offers a supplementary guarantee; in fact, “the law’s procedure allows the intervention of several constitutional institutions; the control exerted by these institutions has a great importance and obviously reflects on the coherence of the texts and on the opportunity to take them”³.

Medical deontology governing experimentation and research on human is also regulated by a decree, namely Decree n°93-1155 dated May 17th 1993 establishing a Code of Medical Deontology⁴. Indeed, this Code is providing for some rules relating to testing and research on humans⁵. Under Article 99 “experimentation on a human being has to respect the moral and scientific principles which justify the research in human medicine”.

It is also worth stating that Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine has been lastly amended by decree n°2001-1076 dated May 14th 2001⁶. Article 6 as amended provides that “any medical or scientific experimentation of medicines intended for the human medicine is subjected to a regime of specifications approved by regulation of the Minister of Public Health”.

Apart from these texts, it is important to mention another one of a great significance, namely the regulation of the Minister of Public Health dated May 28th, 2001 approving the “book of specifications” relating to medical or scientific experimentation of drugs for human medicine⁷. However, the fact of “banishing the guiding principles relating to good practices in clinical trials to the simplest rank of a simple annexed documents to the above mentioned “book of specifications”⁸ is a critical issue. In fact, scholars point out to “the “relative”

¹ R. Ben Hammed, “Moral criteria and legal limits in performing clinical trials in Tunisia”, (Arabic version), Paper offered in tribute to Dean Mustapha Filali, p.8 (pending to be edited).

² Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine, *J.O.R.T* n°60 dated September 21st 1990, p.1354 and as amended by Decree n°2001-1076 dated May 14th 2001, *J.O.R.T* n°40 dated May 18th 2001, p.1141.

³ M. K. Jamoussi, *op. cit.*, p.13.

⁴ Decree n°93-1155 dated May 17th 1993 establishing a Code of Medical Deontology, *J.O.R.T* n°40 dated May 28th & June 1st 1993, p.764.

⁵ See Title VI (articles 99-111) providing for the rules relating to testing and research on human. This Title is divided into two chapters: the first one is on therapeutic experimentation whereas the second is devoted to non therapeutic experimentation.

⁶ Decree n°2001-1076 dated May 14th 2001 amending Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine, in *J.O.R.T* n°40 dated May 18th 2001, p.1141.

⁷ R. Ben Hammed, “Moral criteria and legal limits in performing clinical trials in Tunisia”, (Arabic version), Paper offered in tribute to Dean Mustapha Filali, p.10 (pending to be edited).

⁸ M. K. Jamoussi, *op. cit.*, p.14.

binding force of this document. It is a document of a contractual nature”¹. Its binding force applies only to sponsors and investigators in their relationship with the competent administration. It is deprived of any binding force vis-à-vis third parties, and in particular vis-à-vis the participating subjects.

B - A rigorous content

The legal framework deal with several questions on medical or scientific experimentation of drugs for human medicine, but mainly, the protection of research subjects should be the first priority of any legislation governing clinical trials at least when it comes first to the “informed consent” and second to the scope of application relating to research subjects.

1 - The rigor of the informed consent

Obligation to inform the person who is subject to clinical trials is based on article 22 of Helsinki Declaration. This obligation of information is not sufficient; it must be followed by the “informed consent” expressed unequivocally by the subject of the research. It is worth starting by explaining what is meant by “informed consent”. Article 2 (j) of Directive 2001, gives a clear definition of the “informed consent”. It is a “decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation”². To fully describe participation to a candidate subject, the doctors and nurses involved in the trial explain the details of the study³. The participant then decides whether or not to sign the document in agreement. Informed consent is not an immutable contract, as the participant can withdraw at any time. This notion of informed consent of participating human subjects exists in many countries all over the world, but its application may still vary.

In Belgium, “the ethics Committee will discuss primarily the legitimacy of the proposed research, the safety of subjects for the experiment and the procedure for collecting the informed consent”⁴. In other countries, competent authorities are in charge of scrutinizing the validity of the informed consent. In “Switzerland, it is the Swiss Academy of Sciences who is

¹ M. K. Charfeddine, “La question de l’actualisation des textes relatifs aux essais cliniques”, in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.75.

² Article 2 of the European Directive, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, amended by Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, p. 06.

³ Foreign language translation is provided if the participant's native language is not the same as the study protocol. The research team must provide an informed consent document that includes trial details, such as its purpose, duration, required procedures, risks, potential benefits and key contacts.

⁴ A. Aouij-Mrad, « Droit Comparé : Normes et Pratiques », in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.49.

in charge of this highly serious moral task; in Canada, it is the duty of the Law Reform Commission, which complies with the guidelines of the Medical Council Research”¹.

In Tunisia, Article 5 of Decree n°90-1401 dated September 3rd 1990 stipulates that it is the expert in charge of clinical trials who must explain to the subject of the research the purpose which lies behind his investigations, and their duration and constraints and predictable side effects. The purpose is to inform the patient of his own rights in order for the latter to be able to take his decision to participate or not, being perfectly in due knowledge of all data information. “The role of the expert is limited to the information of the patient as part of what is called the “informed consent application” which must contain the following information: a specification as to the research framework; an overview of the objectives of testing and research methodology to be followed; the responsibilities of participant in the experimentation; the disadvantages and risks of such experimentation, as well as the expected benefits; the other possible modes of treatment, if any; the compensation in case that secondary effects occur after the experimentation; the voluntary aspect of participation and the right to refuse; and the guarantee of confidentiality”².

Thus, under Article 5 of the above mentioned Decree, no medical or scientific experimentation can be implemented without the free, informed and written consent of research subjects and after due communication by their expert clinician of all the information listed above. In addition to the provision mentioned above, articles ranging from 107 till 111 of the Code of Medical Deontology³ relating to non therapeutic experimentation stipulate that consent to undertake experimentation should be: precarious, revocable, free, and given by writing.

However, when it comes to practice, difficulties may arise in case of emergency when the physician must take immediate decision; hence the obligation of informed consent becomes impossible to be fulfilled. Exception to bypass the obligation of informed consent emanating from the patient himself may also be found within legal texts whereby article 2 (last paragraph) of Decree n°90-1401 dated September 3rd 1990⁴ allows that “patients or mental deficient may be subjected to a therapeutic medical experimentation, specific to their disease or deficiency. In that case, the written consent of the legal representative is necessarily required”.

2 - The rigor as to the research subjects

Limits to enrol into clinical trials do exist. Mainly women, children, and people with specific medical conditions are frequently excluded from clinical trials for their vulnerability.

¹ F. Beaufils, “Information et consentement”, in *Les comités de recherche biomédical*, p.171, mentioned by Amel Aouij-Mrad, « Droit Comparé : Normes et Pratiques », in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.50.

² M. K. Jamoussi, « Le cadre juridique et réglementaire des essais cliniques de nouveaux médicaments chez l’Homme en Tunisie », in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.15.

³ Decree n°93-1155 dated May 17th 1993 establishing a Code of Medical Deontology, *J.O.R.T* n°40 dated May 28th & June 1st 1993, pp.769-770.

⁴ Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine, *J.O.R.T* n°60 dated September 21st 1990, p.1355.

Indeed, the presence of protocol exclusion criteria based on comorbid conditions, functional status, and life expectancy explain to a large extent this exclusion¹.

Moreover, elderly are also excluded from clinical trials. Elderly comprise a significant part of the population but they consume over one-third of drugs. Despite this fact, they are often excluded from trials because physicians argue that their bad health issues as well as their frequent use of drugs produce confused data base.

Exclusion from clinical trials is not arbitrary. Apart from logical and moral arguments, “two disparate rationales are in play: beneficence and efficiency”. As far as beneficence is concerned, “persons should be excluded from trials if they cannot be expected to receive no benefit or may be harmed by the treatment. Cancer treatments in particular often involve significant bodily insult from surgery, radiation, or toxic agents. Patients with pre-existing organ system failure or impaired functional status may not be able to tolerate such treatments (NCI 2003). Their exclusion from trials is appropriate if they would not be candidates for therapy in typical practice. Patients with impaired mental function, as from Alzheimer’s disease or psychosis, may be unable to provide informed consent and thus be ineligible for randomization”².

In the second case, efficiency is “quite a different rationale for exclusions, and relates primarily to the interests of investigators and organizations funding research. Unrepresentative enrolment can arise from convenience sampling (e.g. trials conducted in single institutions or locales). Exclusion criteria can be incorporated into protocols for the explicit purpose of increasing the power of the trial to detect treatment effects for a given number of participants (Finn 1999). For industry sponsored trials the objective is to get drugs to market, establishing safety and efficacy is a means to that end. If individuals with poor prognoses and co-morbid conditions are excluded, fewer will be lost to follow-up from deaths due to unrelated causes. Furthermore, the more homogeneous the trial sample is, the less likely are unobserved confounding factors to influence the results”³.

In Tunisia, legal barriers to enrol into clinical trials do exist. Legal texts⁴ are clear in prohibiting experimentations on some categories of persons namely children, pregnant and nursing women as well as patients suffering from mental diseases. These exclusions are absolute but scholars do criticize this categorical and absolute exclusion. Indeed, the absolute exclusion of minors in Decree n°90-1401, article 2 (parag.2 a) is not provided for in other legal texts relating to clinical trials. In fact, Article 24 of Helsinki Declaration allows to undertake clinical trials on minors under the condition of obtaining the authorization of the legal representative, whereas the French legislation allows the possibility of undertaking clinical trials under specific conditions (Fr L.1121-6), and also Directive 2001/20 which only

¹ As an example, and as far as specific trials are concerned, “studies of cardiac trials have found lack of representation for women, minorities, and the elderly”, see Lee PY, Alexander KP Hammill, Pasquali SK, Peterson ED, “Representation of elderly Persons and Women in Published Randomized Trials of Acute Coronary Syndromes”, in *JAMA* 2001; 286:708-13; mentioned by Meredith L. Kilgore, op. cit.

² Ibid, p.7.

³ Ibid.

⁴ Namely Decree of 1990, Code of Medical Deontology and the Tunisian civil Code (namely Code des Obligations et des Contrats).

emphasizes on the vulnerable nature of this category but still allows clinical trials on that specific category¹.

Under Article 2 of Decree n°90- September 3rd 1990, “scientific and medical experimentation of drugs devoted to human medicine could not be undertaken only on adults enjoying all mental faculties and legal capacities. No experimentation can be undertaken on minors, patients or mental deficient people as well as on pregnant or nursing women. Exception is allowed when it comes to persons suffering from mental diseases. These persons may be subjected to medical therapeutic experimentation specific to their disease or deficiency”². In this case, and as stated above, the written consent of the legal representative is compulsory requested.

II- The institutional framework

The institutional framework acts as a genuine “garde-fous” or parapets. It does only exist in few countries. Which countries will we speak about? We will focus on the European and the American contexts as well as the Tunisian one in a comparative approach. The richness of their experience, their contribution, guides us indeed almost naturally first to the European institutional environment completed as mentioned by the American context, before scrutinizing the Tunisian one. Their experiences reveal common points which are important; although some diverge and devote supplementary requirements, in terms of more refined procedures, than others.

Section A examines clinical trials’ institutional framework and how it varies in Europe, in the United States and in Tunisia as a result of wide-ranging governmental bodies called regulatory agencies. It compares and contrasts the rules of the Food and Drug Administration (FDA) in the United States and its equivalent in Europe, the European Agency for the Evaluation of Medicinal Products (EMA) which embodies the regulatory agency within the European Union. We shall wonder whether Tunisia is equipped with a similar regulatory body. Section B consists of a brief analysis of the ethics environment involved with clinical trials at the international level and if any, at the national one, mainly a discussion of ethics committees in these different contexts.

A- A Cautious control endorsed by official bodies

Clinical trials are supervised by appropriate regulatory authorities. The identification of the regulatory agency varies according to the context, mainly the European and the American contexts, as well as the Tunisian one.

1) at the international level

Within the European Union, the regulatory agency is the European Medicines Agency (EMA). The EMA is a decentralised body of the European Union with headquarters in

¹ M. K. Charfeddine, “La question de l’actualisation des textes relatifs aux essais cliniques”, in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.79.

² Decree n°90-1401 dated September 3rd 1990 laying down the procedures for medical or scientific experimentation of drugs for human medicine, *J.O.R.T* n°60 dated September 21st 1990, p.1355.

London. It is composed of six (6) scientific committees including members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the Agency: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT).

The EMEA main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. As far as clinical trials are concerned, the EMEA is responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products through a centralised procedure. Under the centralised procedure, companies submit a single marketing authorisation application to the EMEA. Once granted by the European Commission, a centralised (or "Community") marketing authorisation is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). It is worthy to keep in mind that all medicinal products for human and animal use deriving from biotechnology and other high technology processes must be approved via the centralised procedure¹. The safety of medicines is monitored constantly by the Agency through a pharmacovigilance network².

It is also important to bring to light that the Agency (EMEA) Work Programmes for 2008 and 2009 set out a number of actions relating to clinical trials conducted in third countries. These actions include verification, at the time of the evaluation of the marketing authorization application, that clinical trials carried out in third countries have been conducted in accordance with the required good clinical practice GCP and ethical standards. The format and content of clinical trial protocols³ has been standardized to follow Good Clinical Practice guidance issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is "a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration"⁴. The work Programme for 2008 and 2009 foresees increased good clinical practice GCP inspection including further extension of the good clinical practice (GCP) policy on increasing numbers

¹ The same applies to all human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. Similarly, all veterinary medicines intended for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals have to go through the centralised procedure. Analysis available on: <<http://www.emea.org>>

² The Agency brings together the scientific resources of over 40 national competent authorities in 30 EU and EEA-EFTA countries in a network of over 4,500 European experts. It contributes to the European Union's international activities through its work with the European Pharmacopoeia, the World Health Organization, and the ICH and VICH trilateral (EU, Japan and US) conferences on harmonisation, among other international organisations and initiatives. Analysis available on: <<http://www.emea.org>>

³ (h) 'Protocol': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments; Article 2 of Directive 2001.

⁴ The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. For further development, see <<http://www.ich.org/cache/compo/276-254-1.html>>

of routine inspections as part of the need for greater supervision of the conduct and ethical standards of clinical trials performed outside the European Union.

According to the feedback of the Conference held jointly on 2007 by the European Commission and the European Medicines Agency Conference, “there should be greater transparency of this process, and its outcome, should be described in the EPAR (European Public Assessment Report)”¹. Many of the actions that arise (e.g. transparency in EPARs, increased training and awareness on ethical issues etc.) will have relevance for all clinical trials that form part of marketing authorization applications. The activities of the EMEA² will address the process of clinical development not only at the time of Marketing Authorisation Application (by which time the pre-authorisation clinical trials have mostly been completed) but at earlier stages before and during the conduct of the clinical trials³.

The actions proposed need to encompass all areas of EMEA activity with impact on clinical trials starting with the early activities such as Scientific Advice, Orphan Designation and Paediatric Investigation Plan and continuing through the finalisation of opinions on initial MAAs and clinical trials conducted post-authorisation. Indeed, and before starting clinical trials, extensive pre-clinical studies are conducted. Pre-clinical studies involve (in vitro) test tube and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Hence, in reality, clinical trials appear as being only a small part of the scientific research.

As from 2007, action areas addressed within the scope of EMEA’s responsibilities include also planning and development, namely “clarification of the practical application of ethical standards for clinical trials, considering issues driving the recruitment of subjects in third countries, reviewing the actions available in response to non-compliance, and establish a policy, ensuring links, with other initiatives taken by the EEA Member States in this area, in consultation with the European Commission DG Enterprise and the Heads of Medicines Agencies”.

But the EMEA is only competent at the level of the European Union whereas at the national level, national competent authorities (NCAs) review and authorise clinical trials, review amendments and safety reports, conduct inspections and authorise manufacturing sites in their territories. Following the implementation of Directive 2001/20 /EC in May 2004, the EU Heads of Medicines Agencies (HMA) “established the Clinical Trials Facilitation Group (CTFG)⁴ to coordinate the implementation of the Clinical Trials Directive across the Member States at an operational level and further improve harmonisation of regulatory requirements relating to clinical trials across the Community”⁵.

In addition to that, the EMEA works with the CTFG and with other technical groups on the management of two databases: “the clinical trials database (EudraCT) and the EudraVigilance

¹ European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, Report on the Conference.

² “EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications”, <<http://www.emea.europa.eu/Inspections/docs/22806708en.pdf>>.

³ Idem.

⁴ CTFG is working to establish and improve communication channels within the European medicines network, and to develop and promote harmonised processes and procedures relating to clinical trials within the scope of the duties of the NCAs.

⁵ Its mandate is published on the HMA website <<http://www.hma.eu>>

Clinical Trial Module (EVCTM — a specific module for the electronic reporting of suspected unexpected serious adverse reactions (SUSARs) by sponsors during clinical trials). The EMEA also convenes and chairs the Good Clinical Practice and Good Manufacturing and Distribution Practice Inspectors Working Groups, which contribute towards preparing implementing guidance for the Directives on good manufacturing practice (GMP), good distribution practice (GDP) and good clinical practice (GCP) inspections”¹.

For the sake of comparison, in the United States of America, the regulatory agency is the Food & Drug Administration. The FDA is an agency within the American Department of Health and Human Services. It consists of several centres and offices which are too numerous to be listed herein². The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation. As far as clinical trials are concerned, the FDA is responsible for the advancing of the public health by helping science’s progress through the Good Clinical Practice Program Mission³. The Good Clinical Practice Program is the focal point within FDA for Good Clinical Practice issues arising in human research trials regulated by FDA. The Good Clinical Practice Program “coordinates FDA policies, contributes to leadership and direction through participation in FDA’s Human Subject Protection/Bioresearch Monitoring Council, coordinates FDA’s Bioresearch Monitoring program with respect to clinical trials, working together with FDA’s Office of Regulatory Affairs (ORA), contributes to international Good Clinical Practice harmonization activities, plans and conducts training and outreach programs, serves as a liaison with the HHS Office for Human Research Protection (OHRP) and other federal agencies and external stakeholders committed to the protection of human research participants”⁴.

It is true that when a clinical trial concerns a new regulated drug or medical device (or an existing drug for a new purpose), it is the appropriate regulatory agency for each country where the sponsor⁵ wishes to sell the drug or device which is supposed to review all study data before allowing the drug/device to proceed to the next phase, or to be marketed. But the FDA may audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data)⁶.

¹ <<http://www.emea.europa.eu/meetings/conference.htm>>

² These centres are listed in the official website of the FDA available at <<http://www.fda.gov/AboutFDA/CentersOffices/default.htm>>

³ <<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>>

⁴ <<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>>

⁵ (e) ‘sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial; Article 2 of Directive 2001/20/EC of The European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, amended by Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, p. 06.

⁶ <<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>>

2) at the national level

In Tunisia, the regulatory agency or at least the institution which embodies the task of a regulatory agency as described above is the Pharmacy and Medicines department (Direction de la Pharmacie et des Médicaments, DMP) of the Ministry of Public Health¹.

Before beginning a clinical trial, sponsors and investigators must get from this structure a copy of the “book of specifications”. The aforementioned document duly signed and legalized must be deposited within the DPM together with the specific protocol, the contract signed between the various participants to the experimentation, the informed consent application, written data to the subjects of the clinical trials, and so forth ...²

This regulatory body plays its mission concurrently with the Ministry of Public Health. Indeed, “sponsors and investigators must provide the Ministry with details on the clinical trial’s purpose, name of the participants, the site where the clinical trial is to be held, date of its beginning and ending, the approval of either the committee or the scientific council of the site, the insurance, the contract, and so forth”³.

The described structural framework is not enough. The existing regulatory agencies are in fact not always as effective as may be desired. Indeed, it is presumed that regulatory agencies cannot cover and control all aspects of clinical trials, the role for self-regulation through the compliance with ethics requirements is thus crucial.

B- Vigilant eyes embodied by ethics committees

All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising Ethics committee before permission is granted to run the trial. Ethics committee has discretion on how it will supervise non interventional studies (observational studies or those using already collected data). The appellation of these bodies is different depending on the context, and the burden they bear too.

1) at the international level

As far as the European Union is concerned, the European Directive 2001 provides that Member States shall take the measures necessary for the establishing of Ethics Committees and their running. Article 2 (K) of Directive 2001 gives a legal definition of “ethics committee”. According to the mentioned article, ethics committee is “an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent”.

¹ D. Dargouth, “Essais Cliniques, Aspect Administratif”, in « *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique* », IX Annual Conference, Tunis, September 30th 2005, p.25.

² D. Dargouth, “Essais Cliniques, Aspect Administratif”, op. cit., p.25.

³ D. Dargouth, “Essais Cliniques, Aspect Administratif”, op. cit., p.25.

Indeed, and in order to enhance the crucial importance of ethics committees, Article 3, paragraphs 2 which provides for the conditions to be fulfilled, mentions the most important one namely the condition of approval. In this respect, in order to get ethics committee's approval, a clinical trial may be undertaken only if, "in particular: (a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee (and/or the competent authority) comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored"¹.

Point 11 of the Directive Preamble specifies that as a rule, authorisation should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials. In exceptional cases raising especially complex problems, explicit written authorisation should, however, be required.

Functioning and powers of Ethics Committee are described in Article 6 thereof (same Directive). The Ethics Committee according to point 2 "shall give its opinion, before a clinical trial commences, on any issue requested". When doing so, the Ethics Committee "shall consider, in particular: (a) the relevance of the clinical trial and the trial design; (b) whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified; (c) the protocol; (d) the suitability of the investigator and supporting staff; (e) the investigator's brochure; (f) the quality of the facilities; (g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3; (h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial; (i) any insurance or indemnity to cover the liability of the investigator and sponsor; (j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site; (k) the arrangements for the recruitment of subjects".

Time allotted to procedure in front of the ethics committee must also be respected. The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned². Nevertheless, exception is tolerated in case of trials "involving medicinal

¹ Others conditions specified by Article 3, paragraphs 2 (b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time; (c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded; (d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation; (e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent; (f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

² Point 6 specifies that "Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period laid down in paragraph 5 shall be suspended until receipt of the supplementary information".

products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted”¹.

The European Directive sets up the requirement for a single opinion on ethics per Member State for multi-centre trials. In order to “achieve this single opinion many Member States have put in place appropriate procedures and established provisions for the functioning of the ethics committees based on common guidelines”². The creation of a single ethics committee in the few Member States where legal regulation is hence necessary.

Scholars do criticize the constitution of ethics committees’ membership. The composition of ethics committees should be further defined, consistent with ICH and GCP requirements, and appropriate involvement of medical and other experts and laypersons, including patients, should be established³. The European Directive and its implementation have not changed the status quo as far as the constitution of the membership of ethics committees is concerned. There are no specifications in the Directive on this point, despite it being addressed in the GCP guideline. There are some legal and institutional requirements at national or committee level, but it is not always easy for ethics committees to find the appropriate balance of members or experts, e.g. a mix of medical and lay members, lawyers or philosophers familiar with the fields of clinical trials and of ethics. Further education and training for ethics-committee members and their support staff should be established to reinforce capacity for scientific and ethical review. Quality assurance systems should be put in place to ensure consistency of ethics committees with requirements such as GCP principles. This might include systems for accreditation of ethics committees, self-evaluation, etc⁴.

The composition of ethics committees varies greatly across Member States, and sometimes within the same country, potentially leading to a disharmonised approach to clinical research. Not all EU countries foresee the participation of patients as members of ethics committees, and where this is specified, the level of involvement foreseen varies. Patients can offer a valuable contribution to the ethics committees in different ways, whether acting as members or being consulted as experts on a case-by-case basis⁵.

Ethics requirements encompass - a part from the condition related to the existence of a body steeped in ethics values - other conditions of a substantial kind. Indeed, the principle of free scientific research, which is asserted in Opinion number 10 of the European Group for the ethics of science and new technologies, must be regulated by the right to information granted to each patient, *lato sensu*, by its free assent, by the conservation of its integrity and its intimacy, thus a regulation of the medical progress. The European Directive establishes

¹ For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

² European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.25.

³ European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.29.

⁴ European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.39.

⁵ European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.38.

clear requirements for the role of ethics committees in this regard. The clinical trial patient's is safeguarded through the compliance with the rules on the protection of personal data.

To be ethical, researchers must obtain the full and informed consent of participating human subjects¹. As developed above, informed consent is a legally-defined process of a person being told about key facts involved in a clinical trial before deciding whether or not to participate. Informed consent is clearly a *necessary* condition for ethical conduct but does not *ensure* ethical conduct. It may be hard to turn this condition into a well-defined quantified objective one. Still, a lot of problems must still be resolved to allow ethics committees to perform their duties. Scholars highlight the necessity of a “further standardisation of ethics committees’ requirements for data and application formats (paper or electronic)”. Indeed, “the diversity of these requirements and the complexity of national processes add to the burden on researchers (and on the ethics committee structures), especially where local ethics committees are involved in reaching the single opinion”².

Another problem emerges which is related to poor resources. “In many cases, ethics committees have very limited resources. Members are generally voluntary and perform their committee duties in addition to their principal activities”. The financing of ethics committees is an issue that has been addressed differently in different Member States. In some cases, this has involved the establishment of a fee for application to the ethics committee. Ethics committees consider “that their available resources are often absorbed in the management of paperwork resulting from large numbers of dossiers, substantial amendments, safety reports, etc., and in the maintenance and archiving of records of applications, meeting minutes and deliberations of the committees, and of their procedures”³.

In a different environment, the organisation of committees involved with ethics issues is different although certain ethical principles are the same; they are related to those conducted in humans, as has been outlined in the Belmont Report⁴. These ethical principles include respect for persons, beneficence (the duty to benefit others), and justice, which call for certain ethically required actions or applications. An ethical review is done for the purpose of ensuring that studies are conducted according to these principles and their applications⁵.

In the United States of America, the body invested with ethics principles is called the Institutional Review Board (IRB). Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions. Approval by an Institutional Review Board, or

¹ If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative.

² European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.26.

³ European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, *Report on the Conference*, p.28.

⁴ Ryan KJ, Brady JV, Cooke RE, et al. *The Belmont Report*. Washington, DC: US Department of Health, Education and Welfare, US Government Printing Office, 1979.

⁵ Respect for persons requires informed consent. Beneficence (the duty to benefit others) calls for an assessment of risks and benefits. Justice requires an equitable selection of research subjects. Vanderpool HY. Unfilled promise: how the Belmont Report can amend the Code of Federal Regulations Title 45 Part 46 - protection of human subjects, in *National Bioethics Advisory Commission (NBAC), Ethical and Policy Issues in Research Involving Human Participants*, Vol. II. Section O, 1–20. Bethesda, MD: NBAC, 2001. See also Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical?, in *JAMA* 2000; 283: 2701.

ethics board, is necessary before all but the most informal medical research can begin. The IRB scrutinizes the study in terms of both medical safety and protection of the patients involved in the study before allowing the researcher to begin the study. It may require changes in study procedures or in the explanations given to the patient. A required yearly “continuing review” report from the investigator updates the ethics board on the progress of the study and any new safety information related to the study.

In commercial clinical trials, “the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial. However, the study protocol and procedures have been adapted to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs. Other researchers (such as in walk-in clinics) use independent IRBs”¹.

Even in case where no ethics committee is available, in a clinical trial, the clinicians’ judgment carries a lot of weight. The U.S. Food and Drug Administration bases approval of drugs upon a clinicians’ judgment of who should be in the trial, how to categorize adverse events, and whether there is a drug interaction and the interpretation of specific parameters. These judgments are critical. Investigators are ultimately responsible for all areas of the study, from recruitment and participant selection to event reporting and monitoring”².

2) at the national level

Article 8 of Law n°91-63 dated July 29th 1991³ relating to sanitary organisation provides among other bodies for the creation of a “National Medical Ethics Committee” to act as a public health consultative body. Decree n°94-1939⁴ as amended by Decree n°2001-2133⁵ clarifies in its first article the mission of this consultative body. Under Article 1 of this Decree, “the mission of the National Committee of Medical Ethics is to give its opinion on moral problems raised by research in the areas of biology, medicine and health, either these problems relate to man, social groups or society as a whole. The Committee devotes among others to promulgate the major principles which allow conciliating between technological progress in the above mentioned domains and ethical and legal standards, human values, human rights and the social, economic and cultural realities”⁶.

¹ Information available at: <http://en.wikipedia.org/w/index.php?title=Clinical_trial&action=edit§ion=24>

² Information available at: <http://en.wikipedia.org/w/index.php?title=Clinical_trial&action=edit§ion=24>

³ Law n°91-63 dated July 29th 1991 relating to sanitary organisation, *J.O.R.T* n°55, August 6th 1991, p.1390.

⁴ Decree n°94-1939 dated September 19th 1994, determining the attributions, the composition and the modalities of functioning of the national committee of medical ethics, *J.O.R.T* n°76 dated September 27th 1994, pp.1590-1591.

⁵ Decree n°2001-2133 dated September 10th 2001, amending and completing Decree n°94-1939 dated September 19th 1994, determining the attributions, the composition and the modalities of functioning of the national committee of medical ethics, *J.O.R.T* n°74, September 14th 2001, p.3015.

⁶ The original version is in Arabic language, for the sake of information, the Official Journal provides a french version hereby: L’article 1 dispose que : « le Comité National d’Ethique Médicale a pour mission de donner son avis sur les problèmes moraux qui sont soulevés par la recherche dans les domaines de la biologie, de la médecine et de santé, que ces problèmes concernant l’homme, les groupes sociaux ou la société toute entière. Le Comité s’attache entre autres à édicter les grands principes qui permettent de concilier les progrès technologiques dans les domaines indiqués au paragraphe précédent avec les normes éthiques et juridiques, les valeurs humaines, les droits de l’homme et les réalités sociales, économiques et culturelles ». Decree n°94-1939 dated September 19th 1994, determining the attributions, the composition and the modalities of functioning of the national committee of medical ethics, *J.O.R.T* n°76 dated September 27th 1994, n°76, pp. 1590-1591.

Article 2 of the same decree specifies that “within the framework of its mission, the National Committee of Medical Ethics is in charge of organizing an annual conference during which the important questions related to medical ethics are publicly debated”. The first article of decree of 2001 adds the following clarification whereby the Committee “may also organise colloquiums and seminars about issues relating to medical ethics”¹. Hence, it is worth stating that the Tunisian ethics committee is not a decision-making body neither is this Committee empowered with binding opinion as far as clinical trials are concerned. The Committee’s opinion is passed on by the Minister of Public Health to the authority which asked for it. According to provisions of article 5, “the Committee may be seized by the president of the Chamber of Deputies, the president of Constitutional Council, the president of the economic and social council, a member of the government as well as by an institution of higher education or scientific research or an association of health sciences. Referral demands are sent to the Minister of Public Health who subjects them to the committee”².

Apart from this consultative body, the “book of specifications” approved by the Minister of Public Health Regulation dated May 28th 2001 provides for the existence of a Consultative Committee in charge of clinical trials’ evaluation. The consultation of the committee is compulsory. Indeed, before beginning a clinical trial, it is compulsory to obtain the Committee written favourable opinion concerning the trial protocol, the form of the informed consent, and the serious effects, if any. But still, the composition and the functioning of the Committee are not clearly set up³. Scholars criticize the singular existence of the Committee, they underline the necessity of duplicating it in order to cover all the territory, and emphasize the importance of a relevant structure which encompasses different specialities ranging from physicians to philosophers and jurists.

In Tunisia, few hospitals experienced the creation of an ethics committee inside the hospital where the clinical trial is held. It is the case of the National Institute of Neurology where physicians reported the great difficulties encountered in order to monitor such trials because of the obvious existing clashes and “conflict of interests” among the Committee team⁴. Moreover, it is important to remind that the existing hospitals’ ethics committees have been created on the recommendation of the National Medical Ethics Committee⁵; they don’t have any legal status and may not consequently interfere officially on clinical trials.

¹ The original version is in Arabic language, for the sake of information, the Official Journal provides a french version hereby: L’article 2 du même décret dispose : « dans le cadre de sa mission, le Comité National d’Ethique Médicale est chargé d’organiser une conférence annuelle au cours de laquelle les questions importantes liées à l’éthique médicale sont abordées publiquement ». L’article premier du décret de 2001 ajoute l’alinéa suivant : « Il peut également organiser des colloques et des séminaires portant sur des questions relatives à l’éthique médicale ».

² The original version is in Arabic language, for the sake of information, the Official Journal provides a french version hereby: Art. 5 « Le comité peut être saisi par le président de la chambre des députés, le président du conseil constitutionnel, le président du conseil économique et social, un membre du gouvernement ainsi que par un établissement d’enseignement supérieur ou de recherche scientifique ou une association des sciences de la santé. Les demandes de saisine sont adressées au ministre de la santé publique qui les soumet au comité ».

³ See also M. K. Charfeddine, “La question de l’actualisation des textes relatifs aux essais cliniques”, in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.76.

⁴ M. Kefi, R. Amouri, F. Hentati, “Ethique et essais cliniques en Tunisie : point de vue des investigateurs, expérience de l’Institut National de Neurologie : Expérience de la légalité illégale”, in *Les essais cliniques de nouveaux médicaments chez l’Homme : Impératifs éthiques et cadre juridique*, IX Annual Conference, Tunis, September 30th 2005, p.45.

⁵ S. Douki, Workshops Synthesis, IX Annual Conference, Tunis, September 30th 2005, p.82.

Before putting an end to this section, it is relevant to point out to the difficulties that arise when trying to set a clear identification of the roles and responsibilities of ethics committees and regulatory agencies because of the duplication of work between the two bodies. Comprehensible lines should be drawn in order to avoid confusion in duties¹.

Conclusion

Despite this tremendous legal and institutional framework, instances of unethical clinical trials are not isolated. Indeed, a lot of problems have arisen. Clinical trials are expensive. Costs of trials are often colossal as they comprise both research costs² and incremental treatment costs³. In order to bypass this issue, temptation is great to minimize costs to the detriment of cautiousness and transparency hence weakening clinical trials process. That's why legal and institutional frameworks are necessary. A sort of "garde-fou", they must protect human beings against injuries and harms which might be caused by clinical trials and problems in the ethical conduct of clinical trials. In fact, "cases of trials that did not undergo adequate ethical review or failed to report serious adverse events indicate flaws in the regulation of clinical trials"⁴. Critics highlighted the "lack of voluntary, informed participation and adequately informed consent"⁵.

Another issue is nowadays undermining clinical trials. The phenomenon of globalization renders easy the delocalisation of clinical trials for the sake of minimizing their costs. Wealthy countries move trials to less wealthy countries namely poor or developing countries. Indeed "an estimated 40 percent of all clinical trials now take place in Asia, Eastern Europe, central and south America". Consequences are serious as it appears that unethical trials have occurred in developing countries. In some cases, trials had not been approved by an ethical review committee or institutional review board, or approval had been given for an unethical trial design. "There is no compulsory registration system for clinical trials in these countries and many do not follow European directives in their operations", says Dr. Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organisation tracking clinical trials in developing countries"⁶.

Issues about "the ethics of clinical trials that are sponsored or conducted by groups in industrialized countries but carried out in developing countries have engendered considerable

¹ "NCA assessing the medical and scientific merit of the trial, whereas the ethics committee would determine whether the protocol meets the ethical standards, is in line with the medical practice of a given country, preserves the rights and integrity of trial subjects, and assess the suitability of the site concerned", European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference held on 3 October 2007 at the EMEA, London, Report on the Conference, p.22.

² The research costs include salary support for investigators and support personnel, the costs of data collection and management, and other costs related to the administration of the research project.

³ Incremental treatment costs are associated with more intensive treatment that results from trial participation (i.e. more diagnostic tests, more frequent physician visits). These incremental treatment costs have customarily been borne by third party payers—government or private sector insurers.

⁴ SOMO briefing paper on ethics in clinical trials, "Examples of unethical trials", February 2008, p.3, <<http://www.somo.nl>>

⁵ Idem.

⁶ K. Acharya, "India: Prime Destination for Unethical Clinical Trials", Inter Press Service, December 14, 2007, <<http://www.commondreams.org/archive/2007/12/14/5838>>

controversy”¹. There is no doubt that the international community has an essential role in this regard in order to put an end to immoral practices in undertaking clinical trials keeping in mind that these practices are motivated by economic profits.

¹ H.T. Shapiro, E.M. Meslin, “Ethical issues in the design and conduct of clinical trials in developing countries” in *New England Journal of Medicine*, July 12, 2001; 345(2), pp.139-42.